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Review Article

Efficacy of Pneumococcal Vaccine

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Abstract

Introduction: Disease-associated with streptococcal pneumonia infection affects large number of individual, but it can be prevented through routine vaccination. Although vaccine uptake rated need to be improved significantly to manage adult pneumococcal disease effectively. The availability of new vaccines may help in reduction in pneumococcal disease through increased vaccination rates. All the adult vaccines remain underused worldwide and the physicians give little priority to pneumococcal vaccines for adults on daily basis. They can provide preventive care by ensuring that adult patients get the full benefit of protection against vaccine-preventable diseases, plays a crucial role in immunization therapy and delivery of new routine vaccine by educating public and showing the risks and benefits associated with vaccines.

Aim of the Study: The review aims to study the efficacy of the pneumococcal vaccine in preventive medicine.

Methodology: The review is comprehensive research of PUBMED since the year 1977 to 2016.

Conclusion: By improving the vaccination rate will contribute to reduction in morbidity and mortality associated with pneumococcal disease. Both conjugate and polysaccharide-based vaccine provide extensive serotype coverage and greater access to those in need. According to some study the conjugate vaccination to children is proven to prevent the transmission of pneumococci to adult population. The disease particularly remains burdensome to immunocompromised patients with comorbidities which require direct vaccination approach. It is concluded that most high-risk patient is best served by combination of PCV13 and PPSV23.

Keywords: *Pneumococcal Vaccines; Pneumonia; Pneumococcal Disease; Polysaccharide Vaccine; Conjugate Polysaccharide Vaccine; A Combination of PPSV23 and PCV13 in Series*

Pneumococcal disease

Pneumonia is caused by gram-positive cocci streptococcus pneumonia. This bacterium also causes otitis media, meningitis, and bacteremia in pediatric, elderly and immunocompromised population. Pneumococcal infection is known to be leading cause of pneumonia in children and frequently occur at-risk population such as individuals with diabetes, asthma, chronic obstructive pulmonary disease. Cardiovascular disease, human immunodeficiency virus and sickle cell disease. Fever chills, malaise, dyspnoea and productive cough is typical presentation of pneumococcal infection and untreated case may progress to acute respiratory failure, septic shock, multiorgan and death [1-3].

Thus, this organism causes great impact on morbidity and mortality in adults and children. The vaccines can be used to reduce the rate of pneumococcal diseases. Immunogenic proteins and carbohydrates have been used for vaccine research for the pneumococcal surface antigens [1].

Methodology

We did a systematic search for Efficacy of Pneumococcal Vaccine using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Pneumococcal vaccines, pneumonia, pneumococcal disease, polysaccharide vaccine, conjugate polysaccharide vaccine, a combination of PPSV23 and PCV13 in series.

Polysaccharide vaccines

Capsular polysaccharides

There are chains of 1 of 92 immunologically distinct polysaccharide subunits of pneumococci anchored to its cell wall surface. These polysaccharides provide protection to pneumococci from complement-mediated opsonophagocytosis, the primary mechanism of clearance of pneumococci from lungs. Thus, production of this polysaccharide is necessary for pneumococcal colonization and virulence, making it an apparent early target antigen. These subunits are highly immunogenic and producing antibodies that treat with homologous serotype. The prevalence of any serotypes varies significantly among different continents and providing different levels of protection for vaccinated individuals depending on their location. There it has been monitored internationally since the beginning of their use as a vaccine antigen [4,5].

Polysaccharide vaccines

The vaccines developed earlier against pneumococci contained purified polysaccharide capsules as antigens. The first vaccine developed contained 14 capsular polysaccharide serotypes (14-valent) and provided protection against pneumococcal disease. In 1983, this vaccine was replaced by the current 23-valent vaccine. In 1983, a 23-valent pneumococcal polysaccharide vaccine (PPSV23) was developed, provided 80 - 90% of protection against pneumococcal capsular serotypes causing disease [6].

There are following serotype included in the pneumococcal vaccine [7].

The vaccine is supplied as either a single dose of 0.5 mL or multidose of 5.0 mL to be administered intramuscularly into deltoid muscle or lateral mid-thigh. The common side effects may be mild injection site reaction such as swelling, headache, and fatigue [6].

Adults of 65 years old age or above is recommended to have a dose of PPSV23. Before age of 65 years a single dose of vaccination is recommended for at-risk adults or two doses of PPSV23 separated by at least five years [8].

Vaccine	Serotype Included
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F
PCV7	4, 6B, 9V, 14, 18C, 19F and 23F
PCV10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F
PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

Table 1: *Pneumococcal vaccines serotypes.*

Polysaccharide conjugate vaccines

Vaccines with capsular polysaccharide conjugated to diphtheria toxins were developed to elicit a protective immune response in children under age 2 years. These conjugated antigens generated T-cell dependent antibody response that was effective in children under 2 years of age. They have also proven to have higher antibody titers in high-risk individual immunized with unconjugated vaccines. In 2002, the first 7-valent pneumococcal polysaccharide vaccines were developed which greatly reduced the rate of infection in children under two years age and after introduction of these vaccines, hospitalization due to pneumonia significantly decreased [9,10].

The second conjugate vaccine developed was 13-valent pneumococcal conjugate vaccine (PCV13) contained 7 serotypes in PCV7, 5 and those found in PPSV23 and a unique serotype found in none that is serotype 6A. Therefore, its increased coverage provided broader benefit against pneumococcal infection, and the infection rates significantly dropped. PCV13 was introduced to cover the six most prevalent serotypes that were not included in PCV7. A longitudinal surveillance program of 43 medical centers in US has observed that the only serotype that is 35B, has increased in infection rates is the one not covered in any current vaccine [11].

PCV13 is available as prefilled single dose of 0.5 mL syringe for intramuscular injection in anterolateral aspect of thigh in infants and the deltoid muscle of upper arm in infants, children, and adults. The common side effects of infection may include irritability, reactions at injection site, decreased appetite and sleep, fever, fatigue, headache, muscle and joint pain, chills or rash [12].

Vaccine efficacy and effectiveness

Lack of sensitive and specific diagnostic methods for establishing the diagnosis of pneumococcal pneumonia makes it unreliable. Randomized studies and case-control or indirect cohort studies, maybe partly overcome by using radiographically confirmed pneumonia but this requires much larger sample size or study population with high risk for pneumococcal disease. Also, relatively low incidence of invasive pneumococcal disease a large study population will be required if this should be the endpoint of prospective study. These obstacles may be overcome by use of case-control or indirect cohort studies [13,14].

In a pre-license study of the 14-valent vaccine, according to two randomized controlled trials in South Africa has shown the significant protective efficacy of multivalent vaccines against pneumococcal pneumonia and radiographically confirmed among 9000 young healthy novice gold-miners [14]. In another study in Papua New Guinea, including 12000 persons of age more than 10 years, the risk of overall pneumonia was the same in vaccine as in placebo group but significantly less death rate among those who were vaccinated [15].

Five large studies have been performed post-licensing of 14-valent vaccine in elderly showing conflicting result with two in favor of vaccine and three showing no major difference between the pneumococcal vaccine and control group [16].

The immune response of PPSV23 v/s PCV13

A study was conducted in two age cohorts who had never received a pneumococcal vaccine previously, aged 50 - 59 years and 60 - 64 years. Post one month of the first dose, the response to a single dose of PCV13 was at least as good as a response to PPSV23 for all of the serotypes (non-inferior) and statistically higher for nine of the 13 serotypes. Thus, an overall superior response to single dose of PCV13

was seen throughout the clinical program. The studies also showed that the response to those aged 50 - 59 years (mean 54 years age) was superior to response in 60-64 years cohort for 8 to 12 serotypes common to both vaccines for serotype 6A, a serotype which is unique to PCV13, indicating the importance of age factor in immune response [7].

A follow-up study was conducted 4 years later, and the adults aged 60 - 64 years initially given PCV13 received PCV13 or PPSV23 and those initially given PPSV23 received another dose of PPSV23. All the adults in age group 50 - 59 years were re-vaccinated with PCV13. It is been concluded that the initial vaccination with PCV13 established an immune state that resulted in the recall of anti-pneumococcal response upon subsequent vaccination with either a conjugate or free polysaccharide vaccine. While the initial vaccine with PPSV23 resulted in an immune state in which subsequent administration of PPSV23 vaccine yielded generally lower responses compared with the initial response [7].

Efficacy of PCV13 against invasive pneumococcal disease (IPD) and pneumonia

A CAPITA trail that is a randomized placebo-controlled trial was conducted in Netherlands among 85000 adults aged 65 years from 2008 to 2013 to verify and demonstrate further the clinical benefit of PSV13 in prevention of pneumococcal pneumonia. The result demonstrated 45.6% efficacy of PCV13 against all vaccine-type pneumococcal pneumonia, 45% efficacy against vaccine-type non-bacteremic pneumococcal pneumonia and 75% efficacy against vaccine-type IPD among adults aged 65 years. Although there was no major impact on all-cause community-acquired pneumonia or mortality possibly due to its low proportion attributable to vaccine type pneumococcus (13%) with very less death rated in this population [17,18].

Efficacy of PPSV24 against IPD and pneumonia

The efficacy and effectiveness of PPSV23 against IPD are consistent with protection against IPD in the younger population, and among general older population however, studies of non-bacteremic pneumococcal pneumonia among adult's population have yielded contradictory result. A meta-analysis conducted by Moberley., *et al*. reported the efficacy of PPSV23 against vaccine-type presumptive pneumococcal pneumonia to be 73%. However, out of this the four studies used the current formulation of PPSV2324 concluded that there is no efficacy against pneumonia [19].

Another meta-analysis conducted by Huss., *et al.* showed no efficacy against pneumonia. A randomized trial against pneumococcal pneumonia reported efficacy of 64% among the residents of long-term care facility. A non-randomized 3-year observational study demonstrated 48% efficacy against non-bacteremic pneumonia on a smaller subset of study participants, after excluding PPSV23 vaccination given 45 years before study enrollment. The interpretation of results by Ochoa-Gondar given that primary analysis utilizing the entire study cohort did not find effectiveness against non-bacteremic pneumonia. So, the observational studies have demonstrated the PPSV effectiveness ranging from 50 - 80% for prevention of IPD among older adults and immunocompetent adults with various underlying disorders [20,21].

Combination of PCV13 and PPSV23

In 2013, approximately 13,500 cases of IPD estimated to have occurred among adults aged 65 years and 20 - 25% cases were caused by PCV13 serotype which was potentially preventable with the use of PCV13 in the population 30 and 38% IPD caused by serotype unique to PPSV23. A high proportion of IPD caused by serotypes unique to PPSV23, broader protection, especially against IPD be expected to be provided through both PCV13 and PPSV23. The combined use of PCV13 and PPSV23 for adults is based on immunogenicity studies only [22].

Evaluation of responses second pneumococcal vaccination administered one year after the initial study doses showed that the second dose of PSV13 resulted in similar OPA levels to that observed after the administration of the first dose. However, this is not the same in case of PPSV23 as the subjects received PPSV23 showed lower OPA antibody response after subsequent administration of PCV13 than those who received PCV13 as initial dose [22].

The optimal interval between the dose of PCV13 and PPSV23 depends on several factors such as immune response, safety, risk window for the protection against disease caused by serotypes unique to PPSV23 and practical considerations such as timing for next visit. No single immunogenicity studies evaluate the responses to PCV and PPSV23 administered in series and the optimal time interval between them. The immune responses have been studied after the sequence of PCV7 or PCV13 followed by PPSV23 in interval of 2,6 and 12 months showed that antibody level was higher after PPSV dose than the pre-PCV baseline. Extension of interval between PCV13 and PPSV23 should be carefully considered against increasing risk window. 2 to 6 months intervals between PCV13 and PPSV23 showed equivalent immune response but the reactogenicity was increased with 2-month interval [22].

The implication for use of pneumococcal vaccine among adults.

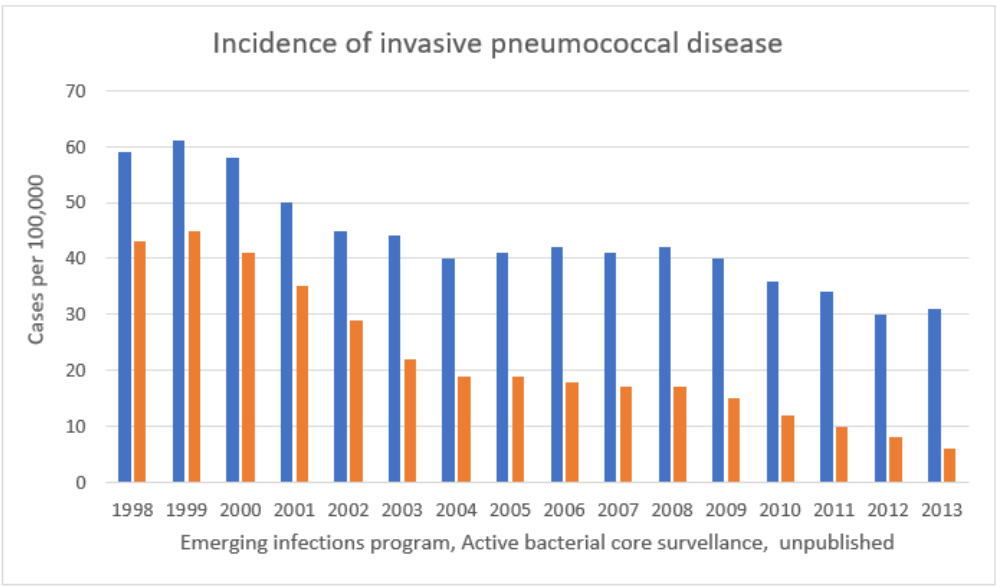

Figure 1: *Changes in the incidence of invasive pneumococcal disease among adults 65 years old, 1998 - 2013. Note Blue bars ¼ IPD caused by all serotypes; red bars ¼ IPD caused by PCV13 serotypes [22].*

There have been substantial reductions in the incidence of pneumococcal disease after the routine vaccination of children with PCV7 began in 2000 and this reduction continued through 2009 till the introduction of PCV13 which further reduced the incidence by 2013 [22].

Conclusion

Advances in vaccine production have provided both conjugate and polysaccharide-based vaccines enabling wider serotype coverage and more access to those in need. The efficacy of polysaccharide vaccine (PPSV23) in prevention of pneumococcal pneumonia especially the elderly age group remain unclear. However, vaccines are proven to be preventive against pneumococcal disease in adults as well as elderly. CAPiTA confirms the efficacy of PCV13 to prevent pneumonia among older adults. The pneumococcal pneumonia prevention of most high-risk adult patient may be best served by combination of PCV13 and PPSV23 provided that PCV13 is given first. Thus, improving the vaccination rates may contribute to significant reduction in morbidity and mortality associated with pneumococcal diseases affecting the population.

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